88-629

No. ———

Supreme Court, U.S.
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IN THE

Supreme Court of the United States

OCTOBER TERM, 1988

UNDETERMINED QUANTITIES OF AN ARTICLE OF DRUG, ANUCORT HEMORRHOIDAL SUPPOSITORIES WITH HYDROCORTISONE ACETATE in any size container in the possession of G & W LABORATORIES, INC., SOUTH PLAINFIELD, NEW JERSEY, Labeled in part: (foil strip) * * * HEMORRHOIDAL-HC SUPP. 0152 * * *

G & W LABORATORIES, INC.,
Petitioner

v.

UNITED STATES OF AMERICA,
Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

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QUESTION PRESENTED FOR REVIEW

Did the Court of Appeals err in affirming summary judgment that the product Anucort is a "new drug" based upon a reading of *Chevron U.S.A. Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984), as requiring deference to the Government's novel interpretation of "new drug" under the Federal Food, Drug, and Cosmetic Act where:

(1) Such interpretation was advanced as an agency interpretation for the first time by Government counsel in this litigation and is contrary to regulatory positions taken by the agency in its regulations and in Federal Register Notices concerning closely related drugs before and since this case was instituted.

(2) The Government's interpretation required, as a matter of law, that the courts ignore the uncontroverted opinions of qualified experts that a product is not a new drug under 21 U.S.C. § 321(p) (i.e., that it is generally recognized among experts as safe and effective based on adequate and well-controlled studies), because those expert conclusions were based on studies conducted with similar products which had not been proven to be bioequivalent to the product in question, although FDA had previously accepted similar extrapolations without bioequivalency data.

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G & W LABORATORIES, INC.,
Petitioner

v.

UNITED STATES OF AMERICA,
Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

The petitioner G & W Laboratories, Inc., respectfully prays that a writ of certiorari issue to review the judgment of the United States Court of Appeals for the Third Circuit entered in this proceeding on August 2, 1988.

OPINIONS BELOW

The decision of the Court of Appeals for the Third Circuit appears as Appendix A. This decision affirmed without opinion the judgment of the United States District Court for the District of New Jersey in *United*

States v. Undetermined Quantities of an Article of Drug . . ., No. 85-523 (August 24, 1987). This decision appears as Appendix B.

JURISDICTION

The decision of the Court of Appeals was entered on August 2, 1988. The Court of Appeals' denial of the Petition for Panel Rehearing was entered on September 7, 1988 (Appendix C). This petition was filed within 90 days of the denial of rehearing under 28 U.S.C. § 2101 (c) and Rule 20.4 of the Rules of the Supreme Court of the United States. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

STATUTES INVOLVED

Because of the length of the statutory and regulatory provisions involved, the relevant portions of 21 U.S.C. § 321(p), 21 U.S.C. § 355(d), 21 C.F.R. § 320.22, and 53 Fed. Reg. 30756 (August 15, 1988), are set out as Appendices D, E, F, and G, respectively.

STATEMENT OF THE CASE

This case involves a controversy over the legal status under the Federal Food, Drug, and Cosmetic Act ("the Act") of Anucort Hemorrhoidal Suppositories ("Anucort"), a prescription drug manufactured by Petitioner G & W Laboratories, Inc. ("G & W"). Anucort is a suppository containing hydrocortisone acetate which is intended for intrarectal insertion to provide topical medication to relieve various local inflammatory conditions such as hemorrhoids. This product has been marketed by G & W since approximately 1958.

Respondent, the United States of America ("the Government"), on November 4, 1985, instituted an *in rem* seizure action against a quantity of Anucort on the grounds that it is a "new drug" for which no new drug

application has been approved. Jurisdiction in the District Court for the District of New Jersey was invoked under 28 U.S.C. §§ 1331, 1345 and 21 U.S.C. § 334. G & W, Petitioner herein, filed a claim as the owner of the seized articles of drug and filed an Answer to the Complaint, along with a Jury Demand, on December 19, 1985.

The precise issue in the case below was whether Anucort is a "new drug" as defined in 21 U.S.C. § 321(p). G & W's principal defense was that Anucort is not within the definition of "new drug" because it is, as required by section 321(p),

> . . . generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling.

Applicable case law, including Supreme Court case law, has established that such general recognition must generally be based on "substantial evidence" which is defined in 21 U.S.C. § 355(d), as including adequate and well-controlled clinical trials. *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 618; 629-30 (1973).[1]

The Government's Summary Judgment Motion was limited to the issue of whether Anucort is generally recognized as effective among qualified experts (safety is not in question), in accordance with 21 U.S.C. § 321(p) as

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[1] This standard applies unless the drug is one for which a finding of efficacy "might be made without [this] kind of scientific support . . ." *See* Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 652 (1973). G & W has also argued that Anucort is such a drug because of its "longstanding market acceptance . . . so that the body of experience alone, without controlled research could support a finding of general recognition." *See* United States v. Articles of Drug . . . Promise Toothpaste, 629 F. Supp. 776 (N.D. Ill. 1984), *aff'd* 826 F.2d 564 (6th Cir. 1987).

interpreted by this Court in *Hynson, Westcott & Dunning*. G & W submitted affidavits of five highly qualified expert physicians which met the requirement of the *Hynson* rule in that they found Anucort generally recognized as safe and effective for its labeled indications based upon specifically identified adequate and well-controlled studies. *See* Joint Appendix on Appeal to the Third Circuit ("J. A."), pp. 39-129. The Government, however, took the novel position that as a matter of law "substantial evidence" for Anucort could only be based on studies with the exact dosage form of the drug involved, i.e., Anucort itself, or on studies with drugs to which Anucort has been shown to be bioequivalent in published studies. The Government relied solely on one supporting affidavit, attesting only to a literature search which revealed no published adequate and well-controlled studies or bioavailability studies conducted with the Anucort product. As stated by the district court, "[b]ioequivalent drugs have similar 'bioavailability,' meaning that the active ingredients in the drugs are absorbed from the drug product at a similar rate and to a similar extent." (*See* Appendix ("App.") 9a, *citing* 21 C.F.R. § 320.1(a), (e).) The affidavit relied on by the Government did not directly address the question of whether Anucort is generally recognized as safe and effective among experts.

The expert affidavits submitted by G & W each attested to the fact that adequate and well-controlled studies with other similar topically applied steroid products (containing hydrocortisone acetate or similar steroids) can be scientifically relied upon to establish the effectiveness of Anucort suppositories without reference to data showing Anucort to be bioequivalent to the other studied drugs.

G & W's experts stated that because of a number of scientific facts applicable to Anucort (and other essentially identical anti-inflammatory drug products), expert recognition of safety and efficacy can and does exist even though there are no published studies specifically with

this product.[2] The experts also cited various statements and rulings of the federal Food and Drug Administration ("FDA") which demonstrate that FDA has itself extrapolated scientific data from one topically-applied steroid product to another in order to find safety and effectiveness without a bioequivalency showing.[3] G & W had sought to discover further evidence of such FDA actions under Fed. R. Civ. P. 56(f), but its requests for such discovery were denied by the U.S. Magistrate.

The district court filed an opinion granting summary judgment on August 24, 1987. The court held that it was required, under *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), to accept the Government's arguments regarding the exact form of evidence (bioequivalency) needed for general recognition of Anucort's efficacy. Specifically, the court deferred to the Government's position on the issues of (1) the need, as a matter of law, for bioavailability studies to establish the general recognition of any product relying on studies with other products; and (2) whether Anucort is a "top-

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[2] The factors relied upon include the fact that hydrocortisone (including hydrocortisone acetate) was the first of a series of effective anti-inflammatory corticosteroid drugs whose activity is well known in the scientific community; the fact that the quantitative effects of topical corticosteroid drugs are well-known and essentially identical; the fact that a large body of medical literature has established that these drugs are effective in treating topical conditions involving a corticosteroid-responsive inflammatory component; the fact that the conditions for which Anucort is recommended include a corticosteroid-responsive component; and the fact that Anucort and drugs of compositions essentially identical to Anucort have been marketed for many years and are well recognized as safe and effective in the medical community. (J.A. 39-129.)

[3] FDA has, for example, formally adopted the position that in vivo bioavailability studies are not necessary for extrapolation of results for a "topically applied preparation." 21 C.F.R. §§ 320.22(a), (b)(2) (App. 27a-28a). *See* I.A. and I.B. *infra* for other examples.

ical" product and thus covered by the principles of FDA's regulation waiving the need for *in vivo* bioavailability studies to show equivalency, 21 C.F.R. § 320.22(b)(2). The fact that highly qualified experts can and did conclude, on the basis of published adequate and well-controlled studies with identical or closely related active ingredients, that Anucort is generally recognized as safe and effective was dismissed by the court as not complying with the Government's interpretation of the nature and form of the studies legally required. Further, the district court dismissed evidence of FDA's prior actions inconsistent with the Government's litigating arguments on both of these issues as mere "transgressions," and upheld the denial of discovery to obtain further evidence to show that deference to the FDA's interpretations of the law on these issues was inappropriate under the *Chevron* case. (App. 13a.)

G & W timely filed a Notice of Appeal to the United States Court of Appeals for the Third Circuit. On August 2, 1988, the Third Circuit affirmed, without opinion, the district court's decision. (App. 2a.)

Subsequent to the Third Circuit's affirmance, FDA issued on August 15, 1988, a Federal Register Notice, 53 Fed. Reg. 30756, in which it stated conclusions factually inconsistent with the legal positions argued by the Government and accepted by the courts below. This Notice casts further significant doubt on the deference to be afforded the Government's litigating "interpretations" of the law in this case. G & W filed a Petition for Panel Rehearing based on this Federal Register Notice, and simultaneously filed for a stay on the mandate pending this petition for writ of certiorari. Petition for Rehearing was denied on September 7, 1988, and issuance of certified judgment in lieu of formal mandate was stayed until October 14, 1988.

REASONS FOR GRANTING THE WRIT

The affirmance by the Third Circuit Court of Appeals of the district court's opinion raises significant questions of federal law as to the proper application of *Chevron U.S.A. Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984). The decision below requires deference to positions taken in litigation by Government counsel which do not represent the agency's established position, contrary to *Church of Scientology v. Internal Revenue Service*, 792 F.2d 153 (D.C. Cir. 1986) (opinion of Scalia, J.), and also confers deference on factual as well as legal issues, subverting the normal due process protection which this Court affords those against whom summary judgment is sought. Determination by this Court of the proper application of *Chevron* in this case will affect innumerable potential litigants and enforcement actions involving federal agencies.

The affirmance by the Third Circuit Court of Appeals of the district court's opinion represents the first time that a Court of Appeals has ruled that as a matter of law, and in all cases, "substantial evidence" requires either studies with the product itself, or bioequivalency data (showing the tested drug to be bioequivalent to the product in question) in order to support general recognition of efficacy of drug products under 21 U.S.C. § 321(p). Such interpretation departs from established precedent which has treated this issue as a triable fact question, rather than one for determination by a court on summary judgment.

Resolution of the issues raised by this decision are important questions of federal law, not resolved by this Court, which will affect manufacturers of all drugs not now the subject of a new drug application ("NDA") or an abbreviated new drug application ("ANDA") filed pursuant to 21 U.S.C. § 355, as well as future administration of the Federal Food, Drug, and Cosmetic Act ("Act") in regulating all such drugs and enforcing the provisions of the Act. One of the FDA's

principal enforcement activities is the identification of all drugs on the market not covered by an NDA or an ANDA for potential enforcement action. FDA has recently identified some 5,000 unapproved marketed prescription drug products potentially within this category.[4]

I. Erroneous Deference to the Government Unduly Broadens the Principles of Judicial Deference Established by This Court.

The opinion below[5] relies virtually exclusively on the doctrine of *Chevron U.S.A. Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984), in which this Court required judicial deference to legal interpretations made by administrative agencies. The lower court's reliance on this doctrine was misplaced for several reasons, and must be reversed to avoid future erroneous applications of *Chevron*.

A. Deference Cannot Apply Where Counsel's Interpretation is Contrary to Prior Agency Conduct.

In this case, the court deferred to the Government's positions on (1) the need for bioavailability studies to establish Anucort's general recognition, and (2) whether Anucort is a "topically applied preparation" and thus entitled to waiver of the *in vivo* bioavailability require-

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[4] *See* House Comm. on Government Operations, *Deficiencies in FDA's Regulation of the Marketing of Unapproved New Drugs: The Case of E-Ferol*, H.R. Doc. No. 98-1168, 98th Cong., 2d Sess. 17 (1984). This House investigation of FDA also cited data indicating that the number of unapproved drugs entering the market has been increasing dramatically over the years. *Id.* at 19.

"Unapproved" is not, of course, equivalent to illegal. Approval is necessary only if a product is a "new drug." This case has important implications for establishing when unapproved drugs are or are not "new drugs" as a matter of law.

[5] Since the Court of Appeals affirmed the district court without opinion, references to the opinion below are necessarily to the district court (App. B).

ment under 21 C.F.R. § 320.22(b)(2). (App. 9a-10a, 11a.)

Application of the *Chevron* doctrine was not proper in this case because the "agency" interpretations relied on by the district court were merely positions taken by the Government counsel for purposes of this litigation. They are not the kind of formal agency interpretations entitled to deference under *Chevron.* As stated in *Church of Scientology of California v. Internal Revenue Service,* 792 F.2d 153, 165 (D.C. Cir. 1986):

> The precept that the agency's rationale must be stated by the agency itself stems from proper respect for the branches of government . . . if courts were to accept an agency counsel's position, they would in effect substitute a judicial interpretation for the agency's.

This in fact is what has occurred in this case, in which Government counsel has taken a novel position for purposes of litigation involving a particular drug, and the district court has granted summary judgment simply in deference to that position, creating a legal precedent where no support for it exists.

Not only did the district court defer to positions adopted for the first time during the course of this litigation, but more importantly, it ignored or dismissed contrary agency interpretations issued with greater formality and authority, in direct contradiction to the *Church of Scientology* opinion:

> Even granting [the principle of deference in *Chevron U.S.A. v. Natural Resources Defense Council,* 467 U.S. 837 (1984)], however, it cannot possibly have application where counsel's interpretation in fact does *not* explain agency action but is, to the contrary, incompatible with the agency's settled course of conduct.

Id. at 162 n.4. This is precisely the situation here, where the Government's only prior pronouncements on the dis-

puted issue were inconsistent with the position it adopted for this litigation.

There were at least two FDA rulings prior to this litigation that bioequivalence studies are not necessarily (i.e., as a matter of law) required to demonstrate effectiveness for drugs similar to Anucort when extrapolating from studies of other drugs. First, FDA's regulations on bioavailability and bioequivalence explicitly exempt certain classes of drugs from the general requirement of demonstrating *in vivo* bioavailability before new drug approval, stating that such evidence is "self-evident or not necessary" for a number of classes of drugs. *See* 21 C.F.R. § 320.22(b)(2). "Topically applied preparations" intended for local therapeutic effect, which is how G & W's experts have categorized Anucort, are one of the classes exempted from bioequivalence requirements. The Government has offered no facts contrary to this classification. It simply relies on the statement in its legal memoranda that FDA does not consider Anucort to be a topical drug. The lower court adopted this factually unsupported position as an agency interpretation and refused to accept the cited regulation as relevant. (App. 11a-12a.)

A second prior FDA ruling relevant to the issue of bioequivalence and ignored by the district court is a Federal Register Notice, 49 Fed. Reg. 11888 (March 28, 1984). (J.A. 139.) This notice explicitly recognizes that it is appropriate to find effectiveness of topical corticosteroids by extrapolating from studies of other corticosteroids. Dr. Harry P. Meyer, Jr., Director of FDA Center for Drugs and Biologics, stated:

> The Director has determined that this finding of effectiveness should not be limited to neomycin in combination with one specific corticosteroid because there is no corticosteroid that is unique with respect to therapeutic and toxic affects. [Citations omitted].

> Therefore, the Director considers the two adequate and well-controlled studies that were submitted in support of the neomycin/fluocinolone combination to provide substantial evidence of effectiveness for the other products listed above, each of which is an ointment, cream, or lotion that contains neomycin with an effective corticosteroid.

The Notice goes on to state that pursuant to 21 C.F.R. § 320.22, bioavailability studies are waived as to applications for approval of these topical preparations.

This ruling by FDA (that evidence of bioavailability is unnecessary for extrapolations by experts between topical corticosteroid drugs) directly contradicts the district court's acceptance of the Government's litigating position that bioequivalency studies are required as a matter of law to extrapolate the results of studies of one drug to another drug. If, as this Court has stated in *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 629-30 (1973), general recognition of effectiveness must ordinarily be based on "substantial evidence," the standard of effectiveness which is applied for approval of new drugs by FDA, then the standard articulated by the FDA in the 1984 Notice should apply to the general recognition of Anucort. At a minimum, the scientific principles stated in that Notice, interpreted in the light most favorable to G & W, establish a factual issue as to whether bioequivalency studies are required for such products.[6]

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[6] In fact, the district court acknowledged FDA's own prior inconsistent actions concerning extrapolation of data, but dismissed such actions as "transgressions" (App. 13a). However, there can only be one standard for substantial evidence which exists "as a matter of law." Where qualified experts agree on the appropriateness of studies "on the basis of which" they may base their conclusions of general recognition of safety and effectiveness, the substantial evidence standard has been met for the purposes of precluding summary judgment. *See* 21 U.S.C. § 355(d).

B. Subsequent FDA Action Relevant to this Case Also Demonstrates that Deference as Applied Below Was Improper.

On August 15, 1988, a Notice of Proposed Rulemaking ("Notice") was published in the Federal Register (53 Fed. Reg. 30756), in the form of a Tentative Final Monograph on Anorectal Drug Products for Over-the-Counter Human Use. The Notice was signed by the Commissioner of Food and Drugs on behalf of the agency. The Commissioner, in a lengthy narrative preamble to the proposed regulations, sets out FDA's position with respect to the law and facts relating to anorectal drug products and listed certain products which FDA accepts as "not new drugs."

In this Notice, FDA made statements which materially contradict the Government's scientific and legal positions adopted by the district court below and affirmed by the Third Circuit. For example, the Government argued at both the district court and appellate levels that anorectal products such as Anucort must, as a matter of law, be shown to be bioequivalent to other anorectal products before general recognition can be based on studies with those products. Thus, on page 17 of its appellate brief ("Gov. Br."), the Government argued:

> Under the rule of [*Hynson, Westcott & Dunning*, 42 U.S. 609] there can, accordingly, be no general recognition of Anucort in the absence of adequate and well-controlled clinical studies on Anucort or, at a minimum, information required in § 355 to show pharmaceutical equivalence and bioequivalence with another product for which there are adequate and well-controlled clinical studies.

The district court opinion had accepted this position on the theory that it was required to defer to FDA's "interpretation:"

> Section 355(d), defining "substantial evidence," does not directly address whether the necessary studies

> must be of the drug product itself. The language employed—". . . investigations . . . on the basis of which it could fairly and reasonably be concluded by such experts that the drug will [be effective]"—is consistent with either party's interpretation. Under such circumstances, *Chevron* dictates that this court accept FDA's interpretation of § 355(d).

(App. 7a.) However, the August 15, 1988 Federal Register Notice states that:

> . . . With regard to the products subject to this monograph, *FDA will not require in vivo bioavailability testing*, but will address product bioavailability in the context of the monograph requirements of (1) appropriate vehicles and other inactive ingredients, and (2) compliance with appropriate good manufacturing practices.
>
> Accordingly, the agency will not require final formulation testing of anorectal drug products covered by a final monograph. Category I anorectal active ingredients may be formulated in appropriate vehicles without additional testing, provided the product is manufactured according to the regulations for the Current Good Manufacturing Practice for Finished Pharmaceuticals (21 CFR Part 211).

53 Fed. Reg. at 30776 (emphasis added). (App. 29a.)

It should be emphasized that FDA is listing these anorectal products as "not new drugs" and permitting their marketing without the submission of *any* bioequivalency or other data. Only if certain requirements dealing with formulations and/or manufacturing procedures are not met will FDA take action. It is clear that under this Notice, no bioavailability "studies" are required, and only good manufacturing practices and appropriate inactive ingredients are needed to avoid new drug status.

Similarly, the Government argued on pages 18-22 of its appellate brief that Section 320.22(b)(2) of its regu-

lations, exempting topical products from bioavailability requirements, does not apply to Anucort because Anucort is not a "topically applied preparation, e.g., a cream, ointment or gel, intended for local therapeutic effect" under the terms of this regulation:

> FDA interprets this provision to apply only to drugs that are applied directly to the site of drug action indicated in the labeling. As it is undisputed that Anucort is a rectal suppository indicated for the treatment of anal conditions, which are outside the rectum, it is not "topically applied . . . for local therapeutic effect" under FDA's interpretation of the regulation, which must be accorded deference. . .

(Gov. Br. at 21-22.)[7] The district court again simply held that it "must defer to FDA's reasonable interpretation of its own regulations," and concluded as a matter of law that Anucort was not exempt under § 320.22 as a topical product. (App. 11a.) However, FDA in the August 15, 1988 Federal Register Notice states specifically that:

> . . . FDA agrees with the comment that final formulation testing should not be required for anorectal drug products *because the products are topically applied* and because, to date, there has been no demon-

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[7] After the district court judgment but prior to affirmance by the Third Circuit, G & W obtained (through the Freedom of Information Act) a ruling by the FDA's Division of Bioequivalence in connection with the approval of an application for an abbreviated new drug approval (ANDA) of an aerosol drug intended for intrarectal administration for the treatment of anal conditions. This product is similar to Anucort in that both are drugs containing hydrocortisone which are intended to be administered intrarectally for treatment of anal inflammatory conditions. This ruling directly contradicts the Government position in this case by stating that such a product is a "topically applied preparation intended for local therapeutic effect," and is therefore deemed bioequivalent to the existing rectal product under 21 C.F.R. § 320.22(b)(2). *See* letter from G & W counsel to Third Circuit Clerk (June 29, 1988) and response by Government counsel (July 8, 1988).

> strated bioavailability problem with any of the products at issue. The in vivo waiver provision of § 320.22(b)(2) for topically applied products reflects the fact that certain topically applied products, that are applied directly to the site of drug action, are less prone to bioavailability problems than are some other drugs and, accordingly, their bioavailability may, in some instances be determined by means other than in vivo product testing. . .

(App. 29a) (emphasis added).

This Notice by its terms applies to anorectal suppositories for intrarectal use, which are specifically referenced in the proposed regulations (*see, e.g.*, proposed § 346.50 (Labeling of anorectal drug products), 53 Fed. Reg. at 30784, ". . . (4) For products for intrarectal use that are wrapped suppositories . . .") Thus, FDA's own very recent application of § 320.22(b)(2) permits rectal suppositories to be declared "not new drugs" without bioavailability studies.

The August 15, 1988 Notice demonstrates that FDA does in fact and in law accept the scientific reasoning urged by G & W and its expert affiants, despite the assertions of Government counsel to the contrary. Further, the Notice also demonstrates the validity of G & W's request for discovery to show that the Government's "legal" arguments are contrary to factual positions which FDA has taken in the past, and which it continues to take in essentially identical situations. This case thus presents precisely the dangers of the *Chevron* doctrine envisioned by *Church of Scientology v. Internal Revenue Service*, 792 F.2d 153, 165 (D.C. Cir. 1986).[8]

Because the district court did not have an opportunity to review this Notice, in which FDA directly contradicts Government positions taken in this case, G & W submits that this Court's power of review should be exercised to

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[8] *See* discussion *supra*, p. 9.

correct the misapplication of *Chevron* in giving deference to legal arguments which misrepresent actual agency practice. The results of this case also represent an opportunity for this Court to define more clearly and to restrict appropriately the application of deference to federal agency interpretations under *Chevron*.

C. The Chevron Doctrine Does Not Apply to Factual Determinations.

The *Chevron* doctrine by its terms applies to legal interpretation and not to factual determinations:

> If Congress has explicitly left a gap [in administering a congressionally created program] for the agency to fill, there is an express delegation of authority to the agency to elucidate a specific provision of the statute by regulation . . . In such a case, the court may not substitute its own construction of a statutory provision for a reasonable interpretation made by the administrator of an agency.
>
> We have long recognized that considerable weight should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer . . .

Chevron at 843-44. In the *Chevron* case, this Court permitted the Environmental Protection Agency to provide its own construction of the congressional "gap" leaving open the precise definition of the term "stationary source" in the Clean Air Act Amendments. (*See Chevron*, 476 U.S. at 843-44.) Subsequent cases applying *Chevron* clearly involve not factual issues but legal interpretations of statutory provisions. *See, e.g., Young v. Community Nutrition Institute*, 476 U.S. 984 (1986) (addressing the question of whether the words "to such extent" in 21 U.S.C. § 346 modify "shall" or the phrase "the quantity therein or thereon").

By contrast, the questions as to which the district court opinion invoked the doctrine in this case were sin-

gularly factual in nature. Specifically, the court deferred to the Government's position on (1) the need for bioavailability studies to establish Anucort's "general recognition" of effectiveness among experts, and (2) whether Anucort is a "topically applied preparation" and thus entitled to waiver of the *in vivo* bioavailability requirement under 21 C.F.R. § 320.22(b)(2). These questions became legal issues only because the Government provided no factual support in the record for its positions, and was unable to counter the factual conclusions presented by G & W experts.

"General recognition" of effectiveness of a drug must be based upon "substantial evidence" as defined in the Act. Substantial evidence is defined in 21 U.S.C. § 355(d) as:

> . . . evidence consisting of adequate and well controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

As is clear from the language of this section, the question of whether particular studies are sufficient to prove effectiveness, i.e., to constitute "substantial evidence," is uniquely dependent upon whether qualified experts can decide that the studies in question are sufficient to support a conclusion of effectiveness.

The district court described the language in section 355(d) as "consistent" with its conclusion that bioequivalency studies are required as a matter of law before data can be extrapolated from a study of one drug product with the same active ingredient to support general recognition of another with the same active ingre-

dient. (App. 7a.) However, there is nothing in the statute to support the district court decision. The statute by its terms requires only such adequate and well-controlled studies as are necessary to support a fair and responsible expert conclusion. The exact nature of such studies is clearly a factual question for determination by scientific and medical experts, not a question of law for attorneys or judges. Whether or not bioavailability or bioequivalency studies are required depends on whether such studies are needed for experts to draw conclusions as to the effectiveness of the particular drug involved.

With respect to its conclusion that Anucort is not a 'topical preparation" covered by 21 C.F.R. § 320.22(b)(2), the district court stated:

> The Government contends that suppositories are not "topically applied preparations"; G & W's experts disagree. Interpretation of this regulation, however, is a matter of law and the court must defer to FDA's reasonable interpretation of its own regulation.

(App. 11a.)[9] Although the court attempted to frame the issue as if it were merely one of statutory interpretation, whether a drug is topical is inherently a factual issue, and deference to FDA was not appropriate in this context. The mere fact that the application of a regulation is involved does not bring an issue within the *Chevron* doctrine. Scientific principles and expert opinion are essential to the determination of "substantial evidence" for purposes of general recognition under 21 U.S.C. § 321(p) and in determining the meaning of "topically applied preparation," and cannot be overridden simply by invoking *Chevron*.

Judicial deference as applied by *Chevron* is appropriate only in the context of judicial review of actions

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[9] The court's decision relating to the need for bioequivalency studies was also specifically based on *Chevron*. (App. 7a, quoted *supra*, pp. 12-13.)

based on an agency's construction of an ambiguous statute. To apply the same deference mandated by that context to factual issues in an enforcement action against the claimant's product, where there has been no administrative determination and where the Government is required under the Act to shoulder the burden of proof, contradicts the most basic due process rights to be accorded a summary judgment opponent.

II. The Decision Below Conflicts with Prior Judicial Applications of 21 U.S.C. § 321(p) and § 355(d).

The district court cited *Premo Pharmaceutical Laboratories v. United States*, 629 F.2d 795 (2d Cir. 1980) in support of its conclusion that bioequivalency studies are always required before data can be extrapolated from one drug product to support the safety and efficacy of another. (App. 8a.) This is a misstatement of the principles applied in *Premo*, and, in fact, conflicts with the legal principles of general recognition applied by the Second Circuit in that case. In *Premo*, there was uncontroverted evidence that differences between the orally administered product in question and the similar product relied upon were such that they might affect safety or efficacy. There was, in fact, an extended trial on the merits involving, inter alia, the adequacy of unpublished bioequivalence data. The Second Circuit based its conclusion of "new drug" status on the existence of a factual showing; namely, ". . . for the undisputed reason that a difference of inactive ingredients, as exists here, when combined with the active ingredient, can affect the safety and effectiveness of the drug product . . ." 629 F.2d at 805.

Thus, contrary to the district court's ruling below, *Premo* does not hold that extrapolation from a study of one drug to another without a bioequivalency study is insufficient as a matter of law on the issue of general recognition. *Premo* does, however, hold that it is inap-

propriate for a Court to weigh the scientific evidence and make its own determination of safety and efficacy. *Id.* This is in essence what the courts below in this case have done by accepting, on summary judgment, the Government's position on the type of scientific evidence required for general recognition of effectiveness, rejecting all of G & W's expert opinions directly contradicting that position.

Other precedents cited by the district court are equally inappropriate since, in each case where products were held to be "new drugs" because of possible bioavailability problems, there was factual evidence that extrapolation from one drug to another would not be appropriate because of the actual differences between the products sought to be compared.[10] In each case, the question was decided as a mater of fact. Thus, for example, in *United States v. Undetermined Quantities of Various Articles of Drugs*, 675 F.2d 994, 1001 (8th Cir. 1982), the court relied on the testimony of a Government witness regarding the need for bioavailability studies as applied to the type of drug product in question, and the district court's findings of fact were sustained only after review of the testimony.

In this case, the courts below failed to apprehend that cases which have held that the products involved were not generally recognized as safe and effective because of possible bioavailability differences do not support a requirement for bioavailability studies as a matter of law, in all cases. This distinction, between finding that bio-

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[10] The case of United States v. Atropine Sulfate 1.0 MG (Article of Drug) . . . Dey-Dose, 843 F.2d 860 (5th Cir. 1988), decided after the district court opinion in this case, upheld a summary judgment decision that the product involved was a "new drug" which could not rely on studies with other products for "general recognition of effectiveness." That decision was, however, based on the fact that no products containing atropine as an active ingredient had ever been approved by FDA. That is not an issue in this case.

equivalency studies are required as a matter of fact, and a legal holding that such bioequivalency studies are always necessary, is an important question of federal law which requires authoritative review by this Court.

III. The Decision Below Requires That the Issue Left Open by This Court in *United States v. Generix Drug Corp.* Now Be Resolved.

The decision of the courts below, purporting to establish the need for bioequivalency studies as a legal requirement before experts can form an opinion on general recognition, presents the issue left unresolved by this Court in *United States v. Generix Drug Corp.*, 460 U.S. 453 (1983), *rev'g* 654 F.2d 1114 (5th Cir. 1981). In the original district court case on review in that case, *United States v. Generix Drug Corp.*, 498 F. Supp. 288 (S.D. Fla. 1980), the Government failed to make a factual showing of the need for bioequivalency studies for two of the eight drug products involved. For the other six drugs in question in that case, the Government did show that there was "some reasonable possibility that differences between the copied drug product and the generic drug product affect the safety and effectiveness of the generic drug product," and on this basis, further distribution of these six products was enjoined. *Id.* at 293-94. For the two drugs for which there was no such showing, the district court denied the injunction sought by the Government.

The defendants appealed the district court injunction affecting its six drugs, but the Government did not cross-appeal as to the other two. The Fifth Circuit reversed the lower court ruling, but was in turn reversed by this Court. In its opinion, this Court specifically noted that since the Government had not appealed the district court's refusal to grant relief as to the other two products, it "had no occasion to pass on" the district court's conclusion that FDA has the burden of showing a "reasonable possibility" that a drug product is not bioequiv-

alent to an approved product in order to have a court enjoin distribution based on alleged "new drug" status. *See* 460 U.S. at 461 n.12.

The unappealed requirement formulated by the district court in *Generix*—that there must be "some reasonable possibility" that the differences between the tested drug and the drug for which "general recognition" is sought will affect safety and effectiveness—is clearly a factual issue and cannot be determined as a matter of law on summary judgment. The district court in this case cited *Generix* for the proposition that "drug" as used in Sections 321(p) and 355(d) refers to the product itself, and not simply the product's active ingredients. (App. 7a.) However, the district court failed to recognize that the lower court in *Generix* treated the issue of the requirement of bioequivalency studies as a fact question, and that this Court had left open the issue of whether the Government must make a showing that different drugs are not bioequivalent before bioequivalency studies are required for a showing of general recognition.[11] If the portion of the district court decision in *Generix* which was left undisturbed by this Court had been applied to this case, summary judgment could not have been granted because of the Government's failure to make any showing of a reasonable possibility of lack of bioequivalence with respect to Anucort.

Resolution of this issue is essential to all future litigation under the Act involving the issue of whether experts may rely on studies with similar or even identical products, even when those studies are in fact "adequate and

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[11] This "open issue" was recently discussed by the Fifth Circuit in United States v. Atropine Sulfate 1.0 MG. (Article of Drug) . . . Dey-Dose, 843 F.2d 860 (5th Cir. 1988) (*see* note 10 *supra*). While noting that the Supreme Court in *Generix* did not decide whether there must be a "reasonable possibility" that products are not equivalent before bioavailability studies are required, the *Dey* decision also failed to answer this question.

well-controlled studies" which establish effectiveness in accordance with 21 U.S.C. §§ 321(p), 355(d), and *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609 (1973). If there must be a showing of "some reasonable possibility" that the difference between drugs will affect safety and effectiveness, then the decision below must be reversed. To reverse and require a positive showing by the Government would be consistent not only with prior judicial interpretations of "substantial evidence" as a fact issue, but would reconcile this case with settled principles of summary judgment established by this Court. As the movant for summary judgment, the Government in this case had the clear burden of identifying specifically the materials that demonstrated the absence of any genuine issue of material fact. *Celotex Corp. v. Catrett*, 477 U.S. 317, 106 S. Ct. 2548, 2554 (1986). Without any positive showing of need for bioavailability studies, and in direct contradiction to the expert testimony offered by G & W, the granting of summary judgment in favor of the Government was inappropriate and denied G & W its right to be fairly and fully heard at trial.

CONCLUSION

For the foregoing reasons, the Petitioner, G & W Laboratories, prays that this Honorable Court grant the instant Petition for Writ of Certiorari and, upon review, reverse the decision of the Third Circuit Court of Appeals, and of the District Court for the District of New Jersey, in holding Anucort to be a "new drug" within the meaning of 21 U.S.C. § 321(p) for purposes of summary judgment, and that the case be remanded to the district court for full discovery and trial on the merits.

Respectfully submitted,

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October 14, 1988

APPENDICES

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 88-5030

UNITED STATES OF AMERICA

v.

UNDETERMINED QUANTITIES OF A DRUG, ANUCORT HC SUPPOSITORIES CONTAINING HYDROCORTISONE ACETATE in any size container in the possession of G&W LABORATORIES, INC., SOUTH PLAINFIELD, NEW JERSEY, labeled in part: (foil strip) "* * * HEMORRHOIDAL-HC SUPP. 0152 * * *"

G & W LABORATORIES, INC., CLAIMANT,
Appellant

Appeal from the United States District Court
for the District of New Jersey (Newark)
(D.C. Civil Action No. 85-5232)
Dist. Judge: Hon. H. Lee Sarakin

Argued July 27, 1988

Before: HIGGINBOTHAM, BECKER and GREENBERG, *Circuit Judges.*

JUDGMENT ORDER

After consideration of all contentions raised by appellant, it is

ADJUDGED AND ORDERED that the judgment of the district court be and is hereby AFFIRMED.

Costs taxed against appellant.

BY THE COURT

/s/ A. Leon Higginbotham
Circuit Judge

Attest:

/s/ Sally Mrvos
SALLY MRVOS
Clerk

Aug. 2, 1988

APPENDIX B

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Civil Action No. 85-5232

UNITED STATES OF AMERICA,
Plaintiff,

v.

UNDETERMINED QUANTITIES OF AN ARTICLE OF DRUG, . . .
(ANUCORT HC SUPPOSITORIES),
Defendants.

[Filed Aug. 24, 1987]

SAROKIN, District Judge.

OPINION

In this action for seizure and condemnation of a drug, the United States moves for summary judgment.

BACKGROUND

"Anucort Hemorrhoidal Suppositories with Hydrocortisone Acetate" (Anucort) is a prescription drug sold to the public for use in treatment of hemorrhoids. G & W Laboratories, claimant herein, began marketing a drug under this label in 1980.

On November 7, 1985, the United States seized an undetermined quantity of Anucort, pursuant to a complaint of forfeiture. The government's amended complaint, filed November 14, 1985, seeks condemnation of

the seized drug on two grounds. First, the government alleges that Anucort is a new drug, as defined by relevant federal statute, that has not been approved by the Federal Drug Administration (FDA). Second, the government alleges that Anucort is a prescription drug under the statute that has been misbranded.

G & W's answer contains several defenses. First, G & W contends that Anucort is not a new drug and therefore not subject to the required FDA approvals. Second, G & W claims that Anucort is exempted from the new drug approval scheme because it was commercially used and sold prior to the statute's enactment date. Third, G & W contends that the court must remand the matter to the FDA for an initial administrative hearing concerning Anucort's status as a new drug. Fourth, G & W argues that FDA's internal enforcement guidelines preclude this action.

On June 11, 1986, the government moved for summary judgment. The government also moved before the Hon. Ronald J. Hedges, U.S. Magistrate, for a stay of discovery pending resolution of the summary judgment motion. G & W cross-moved for a continuance of the summary judgment motion pending further discovery. On October 16, 1986, Magistrate Hedges granted the government's motion for a stay of discovery and denied G & W's motion for a continuance.

G & W appealed the Magistrate's order to this court. On November 24, 1987, at a hearing on the motion, the parties agreed to proceed with the summary judgment motion solely on the ground that Anucort is a new drug because there exists no substantial evidence supporting its safety and efficacy.[1]

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[1] Counsel for the FDA described the ground upon which the motion would be based as the "lack of substantial evidence to form a basis for general recognition," or the "first heading" of its memorandum in support. Transcript of Proceedings, November 24, 1986, at 27:4 to 7.

On February 17, 1987, the court entered an order that 1) reserved decision on G & W's appeal; 2) stated that plaintiff's summary judgment motion would be directed only to "whether there is a lack of substantial evidence to support a finding that the seized drug is generally recognized as effective as contained in Plaintiff's brief in support of its Motion for Summary Judgment"; 3) stating that the government may rely on only one affidavit, to be submitted, "addressing the existence of relevant studies"; 4) granting G & W the right to submit an opposing affidavit; 5) granting the parties leave to depose the respective affiants.

On February 11, 1987, the government submitted the affidavit of Dr. C. Carnot Evans. G & W moved to disregard statements in the affidavit, arguing that its contents violated the court's order. The court, by order dated April 20, 1987, reserved decision on G & W's motion pending its ruling on plaintiff's summary judgment motion. The court also granted G & W the right to depose Dr. Evans and two FDA employees who conducted the literature searches mentioned in Dr. Evans' affidavit.

G & W chose to depose only Mr. Kenter, one of the FDA employees. On May 26, 1987, the court granted G & W's motion to require the government to provide G & W with citations of studies referred to in notes prepared by Mr. Kenter.

The court now considers plaintiff's motion for summary judgment, as reshaped by this procedural history.

DISCUSSION

I. *Substantial evidence*

Before the court is the question of "whether there is a lack of substantial evidence to support a finding that the seized drug is generally recognized." Plaintiff, to

prevail on its motion for summary judgment, must demonstrate that no genuine issue of material fact exists with respect to this question.

"Substantial evidence," in this context, means

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 U.S.C. § 355(d).[2]

At dispute is the nature of the "adequate and well-controlled investigations" required by the above definition. The government contends that § 355(d) requires published studies of the product Anucort itself. G & W contends that studies of other drugs containing the same active ingredient (hydrocortisone acetate) as Anucort constitute substantial evidence under § 355(d).[3]

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[2] Technically, the question before the court is whether Anucort is "generally recognized" as safe and effective by qualified experts, so as to be outside the definition of a "new drug." 21 U.S.C. § 321(p). However, a finding of "general recognition" under § 321(p) must be based on at least "substantial evidence" as defined in § 355(d). *See United States v. Rutherford*, 442 U.S. 544, 549 n. 7 (1978); *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 629, 632 (1973).

[3] G & W also contends that Dr. Evans affidavit erroneously states, at ¶ 15, that there are no such studies of "any product with the same formulation of active ingredients as the Anucort product." The government responds that it was aware of these Anusol studies, but that the formulation of the specific Anusol drugs tested is different than that of Anucort. Furthermore, the studies of Anusol-HC do not purport to be adequate and well-controlled. Even accept-

The court, in evaluating the validity of the FDA's interpretation of § 355, must follow the analysis set forth by the Supreme Court in *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984). If the statutory provision unambiguously expresses Congress' intent on the precise question at issue, the court and the agency must follow the plain language; however, if the provision is silent or ambiguous as to the relevant issue, the court must defer to the agency's interpretation as long as that interpretation is reasonable. See *id.* at 842-33; *Young v. Community Nutrition Inst.*, 106 S. Ct. 2360, 2364 (1986) (applying *Chevron* to an FDA interpretation of the Food, Drug, and Cosmetic Act).

Section 355(d), defining "substantial evidence," does not directly address whether the necessary studies must be of the drug product itself. The language employed—". . . investigations . . . on the basis of which it could be fairly and reasonably be concluded by such experts that the drug will [be effective]"—is consistent with either party's interpretation. Under such circumstances, *Chevron* dictates that this court accept FDA's interpretation of § 355(d).

Furthermore, such a result is consistent with prior judicial interpretation of the new drug provisions of the Act.

As an initial matter, "drug," as used in § 321(p) and § 355(d), refers to the product itself, and not simply the product's active ingredients. *See United States v. Generix Drug Corp.*, 460 U.S. 453, 456-57 (1983). Two

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ing, however, that a genuine issue exists as to the existence of studies of the same formulation of active ingredients, such an issue is not material given this court's holding that studies of drugs other than Anucort may be substantial evidence of Anucort's effectiveness only if 1) the active ingredients are the same and 2) the drugs are demonstrably bioequivalent. *See infra.*

drugs with the same active ingredients, but different inactive ingredients(excipients), may be released into the body at different rates. See *id.* at 455; *Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F. 2d 795, 805 (2d Cir. 1980). For that reason, courts have rejected arguments that studies of approved drugs containing the same active ingredients as a newly marketed product, in and of themselves, constitute substantial evidence that the new product is generally recognized as safe and effective. *See, e.g., United States v. Undetermined Quantities of Various Articles of Drug*, 675 F. 2d 994, 1001-02 (8th Cir. 1982); *Premo Pharmaceutical Laboratories, Inc.*, 629 F. 2d at 805; *United States v. Premo Pharmaceutical Laboratories, Inc.*, 511 F. Supp. 958, 965-973 (D.N.J. 1981); *Pharmadyne Laboratories, Inc. v. Kennedy*, 466 F. Supp. 100, 102-03 (D.N.J. 1979), *aff'd*, 596 F. 2d 568, 570 (3d Cir. 1979).[4]

However, courts have recognized that studies of a "bioequivalent" drug may be used to show safety and effectiveness of a new product. *See United States v. Undetermined Quantities of Various Articles of Drug*, 675 F. 2d 994, 1001-02 (8th Cir. 1982); *United States v. Premo Pharmaceutical Laboratories*, 511 F. Supp. at 985-88; *cf. United States v. Generix Drug Corp.*, 460 U.S. at

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[4] *United States v. Articles of Drug (Lannett)*, 585 F.2d 575 (3d Cir. 1978), cited by G & W, is neither binding nor persuasive authority to the contrary. The Third Circuit, in dictum, supported G & W's position concerning extrapolation of studies. However, two courts within this district have expressly rejected the *Lannett* reasoning as contrary to the Act's intent. *See United States v. Premo Pharmaceutical Laboratories, Inc.*, 511 F. Supp. 958, 973 (D.N.J. 1981); *Pharmadyne Laboratories, Inc. v. Kennedy*, 466 F. Supp. 100, 102-03 (D.N.J.), *aff'd on other grounds*, 596 F. 2d 568, 570 (3d Cir. 1979) (distinguishing, but not expressly rejecting *Lannett*). Furthermore, the Supreme Court's expression that differences in excipients must be considered in evaluating the safety and effectiveness of a new drug, *United States v. Generix Drug Corp.* 460 U.S. 453, 460-61 (1983), is inconsistent with *Lannett*.

461 (not reaching the question of whether two "demonstrably bioequivalent products" might be considered the same "drug"). Bioequivalent drugs have similar "bioavailability," meaning that the active ingredients in the drugs are absorbed from the drug product at a similar rate and to a similar extent. *See* 21 C.F.R. § 320.1(a), (e).

Moreover, a 1984 amendment to the Act introducing a scheme for abbreviated new drug applications (ANDAs) verifies the significance of bioequivalence. 21 U.S.C. § 355(j). Such applications permit approval of new drug products that are closely related to previously approved products. An ANDA will be approved only if it contains "information to show that the new drug is bioequivalent to the [previously approved] drug." 21 U.S.C. § 355(j)(2)(A)(iv). Congress, by establishing an ANDA procedure with a bioequivalence requirement, confirmed that substantial evidence regarding a new product cannot consist merely of studies of a previously approved product containing the same active ingredients.

Neither Congress nor the courts have determined the precise manner by which bioequivalence of two drugs may be established. The government contends first that the Federal Drug Administration (FDA) is the only body capable of properly testing for bioequivalence. *See United States v. Premo Pharmaceutical Corp.*, 511 F. Supp. at 987. Alternatively, the government argues that substantial evidence of bioequivalence must meet the basic statutory definition—that is, adequate and well-controlled, published studies. Given the current record in this matter, the court need not resolve this question. The court holds that bioequivalence must be demonstrated by "substantial evidence" as defined in § 355(d).

Based on the required deference to the FDA's interpretation as well as available precedent, the court holds that, as a matter of law, G & W may satisfy the "sub-

stantial evidence" requirement only by (1) adequate and well-controlled studies of the product Anucort itself or by (2)(a) adequate and well-controlled studies of another drug with the same active ingredients as Anucort and (b) adequate and well-controlled studies demonstrating that the other drug and Anucort are bioequivalent. Dr. Evans' uncontradicted affidavit establishes that G & W can satisfy neither of these requirements. The FDA literature search failed to reveal any published studies of the Anucort product or any studies "relating to the bioavailability of Anucort." ¶ 15. Dr. Evans, based on the results of the literature search and his personal knowledge, opined that no published studies exist of either the Anucort product, ¶ 16, or Anucort's bioavailability, ¶ 17. This affidavit satisfies plaintiff's burden under Rule 56(c) to establish that there exists no genuine issue of material fact and that plaintiff is entitled to judgment as a matter of law. *See Matsushita Electric Inds. v. Zenith Radio Corp.*, 106 S. Ct. 1351, 1356 (1986).[5]

Given this showing by the government, G & W must set forth specific facts showing that a genuine issue exists regarding the substantial evidence question. Fed. R. Civ. P. 56(e); *Matsushita Electric Inds.*, 106 S. Ct. at 1356. The court rejects each of G & W's attempts to raise such an issue.

First, G & W supplies the affidavits of several experts. These affidavits do not contradict Dr. Evans' statements.

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[5] The court denies G & W's motion to strike Dr. Evans' affidavit. The court relies on ¶¶ 15-17, which contain the results of the literature search and the doctor's opinions based on these results that no published studies exist relating to the safety and effectiveness of Anucort itself or to Anucort's bioavailability. Given the court's interpretation of the Act, these statements are not contrary to the court's February 17, 1987 order stating that the affidavit "shall concern the results of a literature search as to whether there are published studies concerning the safety and effectiveness of Anucort."

These experts all state that they consider Anucort to be safe and effective based on published studies showing that hydrocortisone acetate, Anucort's main active ingredient, is safe and effective. See Declaration of Dr. Vincent P. Zarro, ¶¶ 5,6,18; Declaration of Dr. A.W. Martin Marino, ¶¶ 6, 7; Declaration of Dr. Peter J. Wilk, ¶¶ 5,6,7; Declaration of Dr. Steven Z. Brandeis, ¶ 6; Declaration of Dr. Ira Mark Barash, ¶ 7. These experts state also that medical experts have long accepted extrapolation of results from one corticosteriod (the class of active ingredients used in this treatment) to another.

The affidavits do not raise a triable issue of fact regarding the "substantial evidence" question. As stated above, courts have consistently rejected the argument that studies of approved drugs containing the same active ingredients as a newly marketed product, in and of themselves, constitute substantial evidence that the new product is safe and effective. Furthermore, statements that medical experts generally permit extrapolation among active ingredients in this area, even if accepted by the court, do not address the question of bioequivalence, or how the mixture of these ingredients with different excipients affects release of the ingredients into the body.

Second, G & W asserts that a triable issue exists as to whether Anucort is exempted from demonstrating bioequivalence under 21 C.F.R. § 320.22(b)(2). This section waives the requirement for submission of evidence of bioavailability for "a topically applied preparation, e.g., a cream, ointment, or gel, intended for local therapeutic effect." The government contends that suppositories are not "topically applied preparations"; G & W's experts disagree. Interpretation of this regulation, however, is a matter of law, and the court must defer to FDA's reasonable interpretation of its own regulation. *See, e.g., Vineland Chemical Co. v. United States Envtl. Protection Agency*, 810 F. 2d 402, 409 (3d Cir. 1987);

Revak v. National Mines Corp., 808 F. 2d 996, 1002 (3d Cir. 1986). The court concludes, as a matter of law, that Anucort is not exempted from presenting evidence of bioequivalence by 21 C.F.R. § 320.22(b)(2).

Third, G & W attempts to raise a triable issue of fact by maintaining that the FDA "has announced that it is appropriate to extrapolate from studies with one product to demonstrate effectiveness for other similar products." Memorandum in Opposition to Plaintiff's Motion for Summary Judgment, at 14. G & W's argument is premised principally on a March 1984 statement by Harry M. Meyer, Jr., then Director for FDA's Center for Drugs and Biologics. In that statement, dealing with effectiveness of a combination drug containing neomycin as an active ingredient in combination with a corticosteroid similar to that used in Anucort, Meyer stated:

> The Director has determined that this finding of effectiveness should not be limited to neomycin in combination with one specific corticosteriod because there is no corticosteriod that is unique with respect to therapeutic and toxic effects. [Citations omitted.] Therefore, the Director considers the two adequate and well controlled studies that were submitted in support of the neomycin/fluocinolone combination to provide substantial evidence of effectiveness for the other products listed above, each of which is an ointment, cream, or lotion that contains neomycin with an effective corticosteriod.

49 Fed. Reg. 11888, 11889 (1984).

This statement does not raise a triable issue of fact. The statement explains only that corticosteroids, as active ingredients, are equally effective. The statement does not address, however, any questions of bioavailability—that is, how these active ingredients, when mixed with different excipients, are released to the body. Therefore, this FDA statement does not explicitly state that a find-

ing of effectiveness for one drug may be extrapolated to another drug without an analyis of the two drugs bioequivalence.

However, the FDA statement does not indicate that a bioequivalence finding was made in this particular case.[6] Even assuming that FDA did make such a finding in that matter, the law is plain that extrapolation based solely on identical active ingredients is improper—some finding of bioequivalence is required. Given this, FDA's possible transgressions in approving this combination drug are irrelevant to the question of substantial evidence to support a finding of effectiveness of Anucort. Any issue of fact raised by G & W concerning FDA action on the combination drug application is not material to this matter.[7]

G & W, though failing to oppose plaintiff's motion by raising a genuine issue of fact under Rule 56(c), contends also that the court must deny the motion because further discovery is needed. Rule 56(f) permits a party to oppose a summary judgment motion by identifying facts essential to its opposition upon which further discovery is needed.

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[6] The statement indicates that requirements for *in vivo* (in the human body) bioavailability testing were waived by regulation for the drug product at issue. 49 Fed. Reg. at 11890. The government, in their brief, state that "FDA is still required to perform a biopharmaceutical analysis." Memorandum of Law in Reply to Claimant's Response to Motion for Summary Judgment, at 29 n.18. Nowhere does the FDA statement indicate, however, that FDA determined that the two combination products involved in this situation were bioequivalent before FDA permitted the extrapolation of studies.

[7] G & W also points to a January 1982 statement by an associate director at FDA to the effect that studies of effectiveness of a corticosteroid in curing certain conditions will be extrapolated to prove effectiveness in curing other conditions. Such a statement is irrelevant to whether FDA requires substantial evidence of bioequivalence between two different drug products.

G & W states that further discovery is needed to ascertain "evidence of specific instances in which FDA has approved drugs based on extrapolation." Memorandum in Opposition to Plaintiff's Motion for Summary Judgment, at 24. G & W maintains that this information is relevant "depending on how similar the drugs approved by extrapolation are to Anucort." The court rejects G & W's relevance argument. This court has held, as a matter of law, that studies of an approved drug may not be extrapolated to a newly marketed product simply because the new product contains the same active ingredient as the approved drug—some evidence of bioequivalence is required. This principle has been recognized by several courts and is clearly the present position of the FDA. *See, e.g., United States v. 118/100 Tablet Bottles*, No. 86-1353, slip op. at 2,3 (W.D. La. May 18, 1987). G & W could not defeat plaintiff's motion by demonstrating specific instances in the past where FDA may have deviated from the law; as stated above, such past transgressions would not relieve FDA of its statutory duty in this matter.

The court concludes that plaintiff has demonstrated, as a matter of law, that there exists a lack of substantial evidence to support a finding that Anucort is generally recognized as safe and effective.[8] The court further concludes that G & W has not demonstrated a need for further discovery to oppose plaintiff's summary judgment motion on this issue.

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[8] The court, for the same reasons expressed above, rejects G & W's argument that Anucort falls into an exception to the substantial evidence standard enunciated in *Weinberger v. Bentex Pharmaceuticals*, 412 U.S. 645 (1973). G & W's argument in this regard is nothing more than a reformulation of its main argument in a different guise.

The court's holding regarding substantial evidence obviates the need to address plaintiff's argument that Anucort fails to meet the requirements for a "combination drug."

II. *G & W's affirmative defenses*

Plaintiff, to prevail on its motion for summary judgment, must also demonstrate that G & W's affirmative defenses fail as a matter of law.

A. *Grandfather clause*

G & W alleges in its answer that Anucort falls within a 1962 amendment to § 321(p) that provides:

> In the case of any drug, which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by § 201(p) of the basic Act [21 U.S.C. § 321(p)] as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

Pub. L. 87-781, § 107(a)(4) (1962). A drug is exempt from the new drug provisions of the act if four conditions are met: 1) the drug was commercially used or sold in the U.S. prior to October 1962; 2) the drug was not a "new drug" under the pre-amendment Act; 3) the drug was not covered by an effective new drug application prior to October 1962; 4) the drug is currently intended solely for use under conditions prescribed or recommended in its 1962 labeling. *See United States v. Articles of Drug: 5,906 Boxes*, 745 F.2d 105, 108 (1st Cir. 1984), *cert. denied*, 470 U.S. 1004 (1985). This regulatory exemption must be strictly construed, and G & W has the burden of proof as to each condition. See *id.* at 113.

The government may obtain summary judgment dismissing this defense if it can establish that no genuine issue of fact exists for any of the four necessary condi-

tions. The government argues, based on FDA records,[9] that Anucort fails to meet any of the requirements.

G & W responds that the declaration of Carl J. Greenblatt, G & W's founder and chairman of the board, creates a genuine issue of fact that, under Rule 56(c), precludes the grant of summary judgment. The court finds, however, that G & W's grandfather clause fails as a matter of law even upon crediting Mr. Greenblatt's declaration.

The grandfather clause requires that the "drug" must have been commercially sold or used in the United States prior to 1962. Mr. Greenblatt's statement concerning this requirement is as follows:

> Ever since its introduction in 1958-59, G & W has regularly manufactured and distributed an Anusol-HC formula suppository. Originally these drugs were labeled simply as "hemorrhoidal suppositories with hydrocortisone acetate." However, since 1980-81, *the same formula product* has borne the brand name "Anucort" and is called Anucort Hemorrhoidal Suppositories, as well as being sold on a private label basis to some larger customers.

Greenblatt declaration, ¶ 8 (emphasis added). Paragraph 9 of the declaration clarifies that "the same formula product" means "hemorrhoidal suppositories containing hydrocortisone acetate." Thus, G & W's grandfather clause defense rests on the same flawed premise as its "substantial evidence" argument—that Anucort has long

---

[9] The records are referred to in the Declaration of Bruce E. Byer, (Plaintiff's Exhibit 8 in Support of Summary Judgment) and Plaintiff's Response to Claimant's Discovery Requests Related to the 1962 Grandfather Clause (Plaintiff's Exhibit 8 in Reply to Cliamant's Response to Motion for Summary Judgment). The court, in addressing G & W's Rule 56(f) defense, will discuss the propriety of using this information under the court's previous orders.

been recognized as safe and effective because its active ingredient has long been so recognized. As explained above, the term "drug", as used in § 321(p), refers to the product itself, not simply the product's active ingredients. *See United States v. Generix Drug Corp.*, 460 U.S. 453, 456-57 (1983). Even accepting Mr. Greenblatt's declaration, no genuine issue of fact exists as to whether the product Anucort was commercially sold prior to 1962.

Furthermore, Mr. Greenblatt's declaration fails to raise an issue as to whether Anucort is currently prescribed for use in accordance with its 1962 labeling. "Labeling" under the Act means written or printed material affixed to an article or its container, or accompanying the article. 21 U.S.C. § 321(m). The declaration fails to describe the 1962 labeling and no label is affixed as an exhibit. Under these circumstances, G & W cannot demonstrate that the current use conforms to the prior labeling. In fact, the declaration does not even allege that this condition is satisfied.

The court holds that G & W has failed to raise a genuine issue of fact under Rule 56(c) with regard to two essential elements of its grandfather clause defense.[10] G & W also argues under Rule 56(f) that G & W requires further discovery to oppose plaintiff's motion. The court disagrees, and affirms the Magistrate's order denying G & W's request for a continuance.

Rule 56(f) requires a defending party to set forth "facts essential to justify the party's opposition" upon which further discovery is needed. G & W states, with regard to the grandfather clause defense, that it "believes that other relevant information may be in the files of FDA." Memorandum in Opposition to Plaintiff's Motion for Summary Judgment, at 24. More specifically,

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[10] The court makes no ruling concerning the other elements.

G & W seeks discovery of "FDA's records showing the fact of G & W's manufacture of this product prior to 1962." See Reply to Plaintiff's Memorandum in Opposition to Claimant's Appeal from the Magistrate's Order, at 4.[11]

G & W's argument fails. First, plaintiff has now responded to G & W's discovery requests related to the grandfather clause. See Plaintiff's Exhibit 8 in Response. The government's response does not support G & W's position. More importantly, as discussed above, G & W's grandfather clause argument rests on a flawed legal premise—that Anucort is entitled to the defense as long as G & W marketed a product with the same active ingredient prior to 1962. Even if the FDA has documents to verify Mr. Greenblatt's contention that G & W has manufactured "hemorrhoidal suppositories containing hydrocortisone acetate" since 1958, Declaration of Carl J. Greenblatt at ¶ 9, the affirmative defense fails as a matter of law.[12] Denial of a summary judgment motion on Rule 56(f) grounds is not appropriate under these circumstances. *See Hancock Indus. v. Schaeffer*, 811 F. 2d 225, 230 (3d Cir. 1987).

The court grants plaintiff's motion for summary judgment dismissing G & W's grandfather clause defense.

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[11] The affidavit or Richard S. Morey, filed with the motion for a continuance, identifies facts relating to the "substantial evidence" issue, but not the grandfather clause. ¶ 3.

[12] For this reason, the court's consideration of the affidavit of Bruce E. Beyer—despite the court's prior order of February 17, 1987—is not inappropriate. G & W contends that it needs discovery to show that prior to 1962 G & W marketed other products containing Anucort's active ingredient. Mr. Beyer's affidavit is consistent with this fact, ¶ 2(e), Mr. Greenblatt's declaration states it directly, ¶ 9, and the court accepts it as true. G & W requires no further discovery to oppose plaintiff's motion concerning this affirmative defense.

II. *Affirmative defenses seeking remand to FDA*

G & W's other two affirmative defenses seek remand to the FDA for administrative proceedings to determine whether Anucort is a new drug. The court's holding that Anucort, as a matter of law, is a new drug renders these defenses moot. G & W effectively admits this in its brief —"If the [summary judgment] motion is denied, G & W intends to move that the Court remand this case to FDA based on those affirmative defenses." Memorandum in Opposition to Plaintiff's Motion for Summary Judgment, at 26.

CONCLUSION

The court denies G & W's motion to strike portions of the declaration of Dr. C. Carnot Evans.

The court affirms the Magistrate's order dated October 16, 1986, and thereby denies G & W's motion for a continuance of plaintiff's motion for sumary judgment pending further discovery.

The court grants plaintiff's motion for summary judgment.

/s/ H. Lee Sarokin
H. LEE SAROKIN
U.S.D.J.

Date: August 24, 1987

Original to Clerk, U.S. District Court

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Civil Action No. 85-5232

UNITED STATES OF AMERICA,
Plaintiff,

v.

UNDETERMINED QUANTITIES OF AN ARTICLE OF DRUG, . . .
(ANUCORT HC SUPPOSITORIES),
Defendants.

[Filed Aug. 24, 1987]

ORDER

This matter having come before the court on plaintiff's motion for summary judgment; and the claimant having moved for a continuance of plaintiff's motion pending further discovery; and the Hon. Ronald J. Hedges, U.S. Magistrate, by order dated October 16, 1986, having denied claimant's motion for a continuance; and claimant having appealed to said order to this court; and claimant having moved for an order to disregard statements in the affidavit of Dr. C. Carnot Evans; and the court having considered the written submissions and having heard oral argument on said motions; and for the reasons expressed in the accompanying opinion,

IT IS this 24th day of August, 1987, hereby

ORDERED that the Magistrate's order of October 16, 1986 is affirmed and thereby claimant's motion for a

continuance of plaintiff's motion for summary judgment is denied, and it is further

ORDERED that claimant's motion to disregard statements in the affidavit of Dr. Evans is denied, and it is further

ORDERED that plaintiff's motion for summary judgment is granted

/s/ H. Lee Sarokin
H. LEE SAROKIN
U.S.D.J.

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 88-5030

UNITED STATES OF AMERICA,

v.

UNDETERMINED QUANTITIES OF A DRUG, ANUCORT HC SUPPOSITORIES CONTAINING HYDROCORTISONE ACETATE in any size container in the possession of G&W LABORATORIES, INC., SOUTH PLAINFIELD, NEW JERSEY, labeled in part: (foil strip) "* * * HEMORRHOIDAL-HC SUPP. 0152 * * *"

G & W LABORATORIES, INC., CLAIMANT,
Appellant

(D.C. Civil No. 85-5232)

SUR PETITION FOR PANEL REHEARING

Present: HIGGINBOTHAM, BECKER, and GREENBERG, *Circuit Judges*

The petition for rehearing filed by appellant G & W Laboratories, Inc., having been submitted to the judges who participated in the decision of this court and no judge who concurred in the decision having asked for rehearing, the petition for panel rehearing is DENIED.

BY THE COURT:

/s/ [Illegible]
Circuit Judge

Dated: Sep. 7, 1988

APPENDIX D

21 U.S.C.A. § 321(p) (West 1972):

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this chapter it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

APPENDIX E

21 U.S.C.A. § 355(d) (West 1972):

Grounds for refusing application; approval of application; "substantial evidence" defined

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that

clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

APPENDIX F

21 C.F.R. § 320.22 (1988):

§ 320.22 Criteria for waiver of evidence of in vivo bioavailability.

(a) Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in § 320.21(b), may request the Food and Drug Administration to waive the requirement for the submission of evidence demonstrating the in vivo bioavailability of the drug product that is the subject of the application. A request for waiver shall be submitted with the application. The Food and Drug Administration shall waive the requirement for the submission of evidence of in vivo bioavailability if the drug product meets any of the provisions of paragraph (b), (c), or (d) of this section.

(b) For certain drug products the in vivo bioavailability of the drug product may be self evident or not necessary for the product to achieve any of its intended purposes. The Food and Drug Administration shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability of the drug product if the product meets one of the following criteria:

(1) The drug product meets both of the following conditions:

(i) It is a solution intended solely for intravenous administration.

(ii) It contains an active drug ingredient or therapeutic moiety in the same solvent and concentration as an intravenous solution that is the subject of an approved full new drug application.

(2) The drug product is a topically applied preparation, e.g., a cream, ointment, or gel, intended for local therapeutic effect.

(3) The drug product is an oral dosage form that is not intended to be absorbed, e.g., an antacid or a radiopaque medium.

(4) The drug product meets both of the following conditions:

(i) It is administered by inhalation as a gas or vapor, e.g., a medicinal or an inhalation anesthetic.

(ii) It contains an active drug ingredient or therapeutic moiety in the same dosage form as a drug product that is the subject of an approved full new drug application.

(5) The drug product meets all of the following conditions:

(i) It is an oral solution, elixir, syrup, tincture, or similar other solubilized form.

(ii) It contains an active drug ingredient or therapeutic moiety in the same concentration as a drug product that is the subject of an approved full new drug application.

(iii) It contains no inactive ingredient that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

* * * *

APPENDIX G

53 FED. REG. 30776 (August 15, 1988):

* * * *

While it is not clear whether the Panel intended testing of all products, including formulations containing Category I ingredients, FDA agrees with the comments that final formulation testing should not be required for anorectal drug products because the products are topically applied and because, to date, there has been no demonstrated bioavailability problem with any of the products at issue. The in vivo waiver provision of § 320.22 (b) (2) for topically applied products reflects the fact that certain topically applied products, that are applied directly to the site of drug action, are less prone to bioavailability problems than are some other drugs and, accordingly, their bioavailability may, in some instances, be determined by means other than in vivo product testing. With regard to the products subject to this monograph, FDA will not require in vivo bioavailability testing, but will address product bioavailability in the context of the monograph requirements of (1) appropriate vehicles and other inactive infredients and (2) compliance with appropriate good manufacturing practices.

Accordingly, the agency will not require final formulation testing of anorectal drug products covered by a final monograph. Category I anorectal active ingredients may be formulated in appropriate vehicles without additional testing, provided the product is manufactured according to the regulations for the Current Good Manufacturing Practice for Finished Pharmaceuticals (21 CFR Part 211). Manufacturers should be aware that the newness of a dosage, or method * * * of administration or application, or other condition of use * * * may affect the "newness" of a drug. (See 21 CFR 310.(h) (5).)

* * * *

FILED
DEC 22 1988
JOSEPH F. SPANIOL, JR.
CLERK

No. 88-629

(2)

In the Supreme Court of the United States

OCTOBER TERM, 1988

G & W LABORATORIES, INC., PETITIONER

v.

UNITED STATES OF AMERICA

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

BRIEF FOR THE UNITED STATES IN OPPOSITION

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16 pp

QUESTION PRESENTED

Whether proof that a drug is generally recognized by experts as safe and effective for its intended use under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(p), and therefore may be marketed in interstate commerce without the prior approval of the Food and Drug Administration, must be based on adequate, well-controlled, and published clinical studies of either (1) the drug itself, or (2) another drug for which there are such clinical efficacy studies and for which there are adequate, scientific, and published studies showing that it is a bioequivalent to the drug in question.

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OCTOBER TERM, 1988

No. 88-629

G & W LABORATORIES, INC., PETITIONER

v.

UNITED STATES OF AMERICA

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

BRIEF FOR THE UNITED STATES IN OPPOSITION

OPINIONS BELOW

The order of the court of appeals (Pet. App. 1a-2a) is reported at 857 F.2d 1466 (Table). The opinion of the district court (Pet. App. 3a-19a) is unreported.

JURISDICTION

The judgment of the court of appeals was entered on August 2, 1988. A petition for rehearing was denied on September 7, 1988. The petition for a writ of certiorari was filed on October 14, 1988. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

STATEMENT

1. To prevent the marketing of drugs that have not been proved safe and effective, Congress enacted the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. (& Supp. IV) 301 *et seq.*, which establishes a system of premarketing clearance for drugs. The FDCA prohibits the introduction into interstate commerce of any "new drug" unless a new drug application has been approved by the Food and Drug Administration (FDA). 21 U.S.C. (& Supp. IV) 355(a). Under the FDCA, a "new drug" includes all drugs other than those falling within certain limited exceptions. 21 U.S.C. 321(p). To obtain the FDA's approval, a drug manufacturer must prove, based on scientific evidence, including adequate well-controlled clinical studies, that a drug is safe and effective for its intended use. 21 U.S.C. (& Supp. IV) 355; see *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973).

A drug is not considered a "new drug," and thus is exempt from the premarketing approval requirement, if it is "generally recognized, among experts qualified by scientific training and expertise to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. 321(p) (the general recognition exception). In *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, *supra*, this Court held that a drug cannot be marketed under that exception unless its safety and effectiveness are supported by the same type of scientific evidence necessary to obtain the FDA's approval under 21 U.S.C. (& Supp. IV) 355 to market a new drug. 412 U.S. at 632.

When the drug product is claimed to be a generic copy of one already approved by the FDA, the sponsor may file

with the FDA an "abbreviated new drug application" (ANDA), which relies on the established safety and effectiveness of the previously approved drug. The FDA will approve an ANDA where the generic drug is shown to be the therapeutic equivalent of the approved pioneer drug, and therefore is safe and effective in accordance with 21 U.S.C. (& Supp. IV) 355(d). *Premo Pharmaceutical Laboratories, Inc.* v. *United States,* 629 F.2d 795, 799 (2d Cir. 1980). Therapeutic equivalence is shown by bioequivalence. 21 U.S.C. (Supp. IV) 355(j)(2)(A)(iv). Bioequivalence, in turn, is the ability of two different drug products to deliver the same active ingredients to the site at which the drug is to have its effect, at the same rate and to the same extent. 21 U.S.C. (Supp. IV) 355(j)(7)(B); *Premo,* 629 F.2d at 799 n.4. See also Pet. App. 9a.

2. In the early 1980's, petitioner introduced its prescription drug Anucort Hemorrhoidal Suppositories (Anucort) onto the market. Pet. App. 3a.[1] Petitioner did not seek the FDA's approval for that drug, nor has petitioner ever conducted and published any study of Anucort showing that it is safe and effective for its intended use, or that it is the bioequivalent of another drug that has been demonstrated to be safe and effective.

In November 1985, the government brought this in rem action under 21 U.S.C. 334 to seize a quantity of Anucort, on the ground that it was an unapproved new drug and therefore cannot be marketed in interstate commerce. The

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[1] Anucort contains (among other ingredients) hydrocortisone acetate, a steroid. It is a prescription drug because it is not safe for use except under the supervision of a licensed practitioner. See 21 U.S.C. 353(b)(1)(B). Petitioner marketed another product before 1980 that petitioner claimed was the same drug as Anucort, but petitioner offered no evidence that its earlier product had the same ingredients as Anucort, or that it was labeled for the same uses. Pet. App. 16a-17a.

government moved for summary judgment based on evidence that no adequate, well-controlled, and published clinical investigations had been performed on Anucort, and that there was no published evidence that Anucort was bioequivalent to another drug for which such studies existed.[2] The government argued that, absent such evidence, Anucort could not be generally recognized as safe or effective under 21 U.S.C. 321(p). In response, petitioner submitted affidavits from experts attesting to the safety and effectiveness of Anucort. Petitioner's experts, however, did not base their conclusions on published clinical studies of Anucort. Instead, petitioner's experts relied on studies that had been conducted on other products also containing steroids as active ingredients. None of these experts addressed the issue whether Anucort was shown to be bioequivalent to the drugs on which the experts based their conclusions. Pet. App. 3a-5a.

The district court granted the government's motion for summary judgment. Pet. App. 3a-19a. The court agreed with the FDA that Anucort could not fit within the general recognition exception unless adequate, well-controlled, and published clinical studies on Anucort established its efficacy or unless there were published studies showing that Anucort is bioequivalent to another product for which there are such clinical efficacy studies. *Id.* at 9a-10a. Since petitioner had presented no evidence to rebut the FDA's showing that no such clinical efficacy or bio-

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[2] The government also moved for summary judgment on the alternative ground that there is no consensus of expert opinion on the question whether Anucort is safe and effective. See *United States* v. *Atropine Sulfate 1.0 Mg. (Article of Drug) Dey-Dose*, 843 F.2d 860, 862 (5th Cir. 1988) (*Dey*) (describing the two-step showing necessary to prove that a drug is not a new drug). The district court, however, did not address that issue.

equivalency studies on Anucort existed, the court granted summary judgment for the agency. *Id.* at 10a-14a.

3. The court of appeals summarily affirmed the district court's decision. Pet. App. 1a-2a.

ARGUMENT

The courts below correctly held that Anucort cannot be marketed under the general recognition exception of 21 U.S.C. 321(p) in the absence of adequate and well-controlled studies establishing the effectiveness of that drug, or, at a minimum, scientific evidence that Anucort is the bioequivalent of another drug product for which such clinical efficacy studies exist. Because the court of appeals' decision is correct and does not conflict with any decision of this Court or of another court of appeals, review by this Court is not warranted.

1. The gravamen of petitioner's argument (Pet. 16-18) is that the issue whether a drug is generally recognized as safe and effective is inherently a factual, not a legal, question. Petitioner contends that the district court erred both in deferring to the FDA's judgment about the type of evidence that is necessary to establish safety and efficacy, and in failing to consider the opinions of petitioner's experts that Anucort is safe and effective. And petitioner claims that, even though its experts relied on studies showing only that one of the active ingredients in Anucort, but not Anucort itself, is safe and effective, and did not rely on clinical studies showing that Anucort is bioequivalent to another drug of proven safety and effectiveness, petitioner was entitled to a trial on the merits of its claim that Anucort is generally recognized as safe and effective. That argument lacks merit, for several reasons.

In *Hynson,* this Court ruled that 21 U.S.C. (& Supp. IV) 321(p) and 355 must be interpreted consistently and re-

quire the same type of proof that a drug is safe and effective before it can be marketed in interstate commerce, whether the drug is approved by the FDA or is shown to be exempt under the general recognition exception. The Court therefore concluded that "a drug can be 'generally recognized' by experts as effective for intended use within the meaning of the Act only when that expert consensus is founded upon 'substantial evidence' as defined in [Section 355(d)]." 412 U.S. at 632. And in *United States* v. *Generix Drug Corp.*, 460 U.S. 453 (1983), this Court held that the "drug" that must be generally recognized as safe and effective under 21 U.S.C. 321(p) is the entire product itself, not just its active ingredients. That is because the effects of a drug product cannot be predicted from its active ingredients alone. For example, inactive ingredients added to bind the product (known as "excipients") may affect the rate at which the active ingredients are delivered to a diseased organ and thereby affect the safety or efficacy of the entire drug product. *Generix*, 460 U.S. at 455; *Premo*, 629 F.2d at 799.

It follows from *Hynson* and *Generix* that the clinical studies establishing safety and effectiveness must relate to the product, and not just its active ingredients. The FDA has accordingly concluded that the requirement in 21 U.S.C. (& Supp. IV) 355(d) of studies from which "it could fairly and responsibly be concluded" that a drug is effective means that there must be published clinical efficacy studies on the product itself, or, at a minimum, published clinical efficacy studies of another drug combined with published scientific evidence that the studied drug is bioequivalent to the drug sought to be marketed.[3]

[3] The FDA argued below that all bioequivalence determinations should be left to the agency, which has the expertise to make that determination, rather than the courts. The district court held that if general recognition of Anucort is to be based on its bioequivalence to another drug product, that recognition must be based on adequate,

Congress has confirmed the FDA's interpretation of Section 355(d) in the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585. That Act established an abbreviated approval mechanism for the generic counterparts of drugs that have already been found to be safe and effective by the FDA. To obtain the FDA's approval of a generic drug under that mechanism based on the generic drug's similarity to an already approved drug, rather than on adequate and well-controlled studies submitted by the generic applicant, the Act requires the manufacturer of the drug to show that its generic drug is the bioequivalent of the approved drug. 21 U.S.C. (Supp. IV) 355(j)(2)(A)(iv); see *Denial of Citizen Petition No. 85P-0421/CP (F.D.A. Sept. 29, 1986)*, slip op. 3 (ruling that new Section 355(j)(2)(A)(iv) requires "that everyone who wishes to market a generic drug submit evidence to the agency, as part of an ANDA, that the generic drug is bioequivalent to the pioneer").[4] Congress also made clear in the 1984 amendments that the generic drug manufacturer must bear the burden of showing in all cases that its drug is the bioequivalent of an approved drug, and that the FDA is not required to prove the contrary. 21 U.S.C. (Supp. IV) 355(j)(3)(F).[5]

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well-controlled, and published studies demonstrating bioequivalence. Pet. App. 9a-10a. Since petitioner's experts did not base their analysis of Anucort on any published assessment of its bioequivalence with another drug product, this case does not provide an opportunity to resolve the question whether a district court should ever undertake to determine itself whether one drug is the generally recognized bioequivalent of another.

[4] We have filed a copy of that decision with the Clerk and have provided a copy to counsel for petitioner. The only exception to that requirement involves the substitution of one active ingredient in a drug product containing more than one active ingredient. That exception, however, is not applicable here.

[5] This Court in *Generix* did not decide whether the FDA must bear the burden of going forward to show a need for bioequivalence. 460

Furthermore, it is well settled that when the question is whether a drug is generally recognized as safe and effective, the FDA does not bear the burden of showing that the drug is in fact unsafe or ineffective. The only question for a court to decide is whether the drug is generally recognized as safe and effective based on published studies, and not whether it is safe and effective in fact. See, *e.g.*, *United States* v. *Undetermined Quantities of Various Articles of Drug*, 675 F.2d 994, 999-1001 (8th Cir. 1982), cert. denied, 460 U.S. 1051 (1983); *Premo*, 629 F.2d at 803-804; *United States* v. *1,048,000 Capsules, More or Less, Afrodex*, 494 F.2d 1158, 1160 (5th Cir. 1974); *Tyler Pharmacal Distributors, Inc.* v. *HEW*, 408 F.2d 95, 99 (7th Cir. 1969). The same rule should apply when the question is whether one drug is the bioequivalent of another drug of proven safety and effectiveness. In this context, the only question for a court to decide, as the Second Circuit held in *Premo*, 629 F.2d at 803-804, is whether the drug at issue is generally recognized, based on published studies, as the bioequivalent of the comparison drug, not whether the drug at issue is a bioequivalent in fact.

Finally, the FDA's interpretation of the substantial evidence requirement in Section 355(d) is also supported by important policy concerns. Just as the determination whether a drug is effective cannot rest on the knowledge and experience of individual physicians (see *Hynson*, 412 U.S. at 619 (footnote omitted) ("The hearings underlying that 1962 Act show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous.")), neither can it rest on unverified assumptions that drug products with the same active ingredients

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U.S. at 461 n.12. Congress, however, has answered that question in the 1984 amendments by requiring the manufacturer to establish bioequivalence. Petitioner therefore errs in stating (Pet. 21-23) that this case provides an appropriate vehicle to answer the question left open in *Generix*.

will have the same effects. Because of the limited resources available to the FDA, saddling the FDA with the burden of demonstrating the absence of bioequivalence for the thousands of generic drugs on the market would seriously impair the agency's ability to safeguard the public health. By contrast, it is eminently sensible to require a drug manufacturer to establish that its product is the bioequivalent of another product which it claims to be the therapeutic equivalent, since the manufacturer is the party exposing the public to the product.

In sum, the courts below correctly concluded that petitioner was required to show, based on published studies, and not just the opinions of its own experts, that Anucort is generally recognized as the bioequivalent of a drug of proven safety and effectiveness. Because petitioner offered no such evidence, the district court correctly entered judgment in the agency's favor.

2. Petitioner also contends (Pet. 8-19) that the FDA has taken inconsistent positions on the question presented by this case. In support of this argument, petitioner relies on an FDA regulation, 21 C.F.R. 320.22(b)(2), and two Federal Register notices citing that regulation, 49 Fed. Reg. 11888 (1984), and 53 Fed. Reg. 30756 (Aug. 15, 1988). None of those materials, however, supports petitioner's claim.

The regulation and 1984 Federal Register notice only state that, under certain circumstances, the FDA may waive its general policy of requiring that bioequivalence be shown by an in vivo study and may instead accept some other proof of bioequivalence. See *Dey*, 843 F.2d at 863.[6]

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[6] See 21 C.F.R. 320.22(b) (the FDA "shall waive the requirements for the submission of *evidence obtained in vivo*" in certain specified circumstances) (emphasis added). The 1984 Federal Register notice also refers to the waiver of only in vivo studies.

The FDA's regulations authorize the agency to accept other types of bioequivalence analyses. 21 C.F.R. 320.53. The FDA has concluded

The regulation and notice do not state that the FDA can or will waive the statutory requirement that a drug manufacturer establish bioequivalence in some manner, and the 1984 amendments do not permit the FDA to waive that requirement. *Denial of Citizen Petition,* slip op. 3.[7]

Moreover, neither the regulation nor the 1984 Federal Register notice applies to a drug like Anucort. The regulation allows the FDA to waive the in vivo study requirement only for a "topically applied preparation, e.g., a cream, ointment or gel, intended for local therapeutic effect." 21 C.F.R. 320.22(b)(2). Anucort cannot qualify under that regulation, since it is undisputed (and petitioner concedes, Pet. 2) that Anucort is a suppository that is applied internally to the rectum, even though it is labeled for use in connection with external conditions. The regulation, however, refers to a drug that is applied directly to the site at which the drug is to have its effect, such as an antibiotic ointment that is applied directly to a wound, which does not include Anucort.[8]

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that, rather than rely on in vivo testing of the final product, the agency can in some limited classes of cases rely on product formulation and chemistry and the manufacturing process, which are the primary factors affecting bioequivalence. See *United States* v. *Premo Pharmaceutical Laboratories, Inc.,* 511 F. Supp. 958, 980-985 (D.N.J. 1981). The 1988 Federal Register notice cited by petitioner makes that point. It states that the FDA "will address product bioavailability in the context of the monograph [proposed rule] requirements of (1) appropriate vehicles and other inactive ingredients and (2) compliance with appropriate good manufacturing practices." 53 Fed. Reg. 30776 (Aug. 15, 1988).

[7] Even if the regulation and notices permitted a drug manufacturer to show that its product is generally recognized as safe and effective based on scientific studies other than in vivo studies, petitioner still could not prevail, because it is undisputed that there are no published bioequivalence assessments of any kind involving Anucort.

[8] The FDA's interpretation of its regulation is consistent with the position that the agency took in the 1988 Federal Register notice on

Petitioner's reliance on the 1988 Notice of Proposed Rulemaking is also misplaced. That proposed rule addresses a limited class of over-the-counter drug products that are deemed by FDA to be generally recognized as safe and effective within the meaning of Section 321(p). 53 Fed. Reg. 30756. Anucort is a prescription drug (page 3 note 1, *supra*), not an over-the-counter product, and therefore would not be affected by the new rule. Moreover, the proposed rule specifically excludes rectal suppositories that, like Anucort, are offered for external uses.

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products like Anucort (53 Fed. Reg. 30773 (Aug. 15, 1988)):

> The comment is correct in stating that the Panel did not recommend labeling for the intrarectal application of suppositories and ointments containing a local anesthetic to relieve pain stemming from irriation outside the rectum (i.e., in the anal canal below the mucocutaneous junction and perianal area). Although the comment contends that such an intrarectal application would be effective because of liquefaction of the product and subsequent seepage through the anal canal, the Panel considered seepage only within the context of an incontinent anal sphincter and not within the context that an incontinent anal sphincter would provide a means to relieve external symptoms on the skin of the perianal area and the anal canal. Rather, the Panel considered intrarectal application only for local effect inside the rectum. The comment provided no data to alter the Panel's recommendations, and the agency believes that the intrarectal application of a suppository or ointment is not an appropriate means to alleviate external symptoms through liquefaction and seepage.

There is thus no merit to petitioner's argument that the FDA's construction of its own regulation is not entitled to deference since that position was first adopted during the course of this case. And even if the issue had only emerged in this case, it is not clear that FDA's construction should be entitled to no deference. See *United States* v. *Morton*, 467 U.S. 822, 835-836 n.21 (1984) ("Litigation often brings to light latent ambiguities or unanswered questions that might not otherwise be apparent."); *Gardebring* v. *Jenkins*, No. 86-978 (Apr. 19, 1988), slip op. 13-14.

Finally, the proposed rule does not apply to products, like Anucort, that contain steroids as active ingredients.

3. Contrary to petitioner's contention (Pet. 19-21), *Premo Pharmaceutical Laboratories, Inc.* v. *United States, supra,* does not conflict with the decision below. *Premo* flatly rejected the drug manufacturer's claim that a district court, when determining whether a drug is generally recognized as safe and effective under Section 321(p), may decide whether the drug is in fact safe and effective for its intended use based on its bioequivalence to another drug. The Second Circuit held that the only question for a court to decide is whether published scientific data, including any bioequivalency studies, establish a consensus that the drug is generally recognized as safe and effective. 629 F.2d at 803-804. *Premo* therefore firmly supports the conclusion that the only question before the district court in this case was whether published scientific data showed that Anucort was the bioequivalent of another drug of proven safety and effectiveness, and that the district court was not authorized to make the bioequivalence determination as a question of fact. Since that is precisely what petitioner sought to do in this case, *Premo* supports the court of appeals' decision.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

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OCTOBER TERM, 1988

G & W LABORATORIES, INC.,
Petitioner,

v.

UNITED STATES OF AMERICA,
Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Third Circuit

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PETITIONER'S REPLY BRIEF

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PETITIONER'S REPLY BRIEF

Petitioner G & W Laboratories, Inc. (G & W) submits this brief in reply to the brief of the Government in opposition to G & W's petition for a writ of certiorari. The brief addresses issues newly raised in the Government brief.

ARGUMENT

1. The Government brief fails to respond to G & W's arguments that in the courts below there was erroneous deference in reliance on *Chevron U.S.A. Inc. v. National Resources Defense Council*, 467 U.S. 837 (1984) to litigating positions taken by FDA which are inconsistent

with other administrative actions which FDA took prior to this case and also with a recently promulgated FDA Notice of Proposed Rulemaking.

The only partial response on this question comes at the end of footnote 8, citing the *Morton* and *Gardebring* cases for the proposition that an agency's position is not necessarily to be disregarded because the agency first took the position in response to the litigation in question. While this may be true, neither case addresses a situation in which the agency's litigating position is directly contradictory to other agency decisions, taken both before and after the litigation. Both *Morton* and *Gardebring* involve situations in which the agency wrote on a clean slate, not one in which its litigating position is inconsistent with other agency actions. Here the agency is contending that, as a matter of law, studies with one product cannot support the effectiveness of another unless there is actual bioequivalence data available to show equivalence between the two products. That is a factual question which the FDA has in fact decided differently in other contexts, see petition, pp. 10-16.

G & W points out in its petition (pp. 12-16) that the FDA took actions in its 1988 Notice of Proposed Rulemaking on Anorectal Drug Products which demonstrate that the deference to FDA's position below was improper. On pages 10-11 of its brief, the Government argues that the 1988 Notice does not apply to Anucort for various reasons and should not be relied upon by the Court.

G & W never suggested that the 1988 Notice applies directly to Anucort. It only pointed out that the Notice contained a number of FDA statements on scientific and legal positions which are contrary to the agency positions asserted in this case to which the courts below gave deference under the *Chevron* doctrine. In any event, it should be noted that in footnote 8, the Government brief refers to the same 1988 notice as "the 1988 Federal

Register Notice on products like Anucort" and also relies on the Notice in footnote 6, at the same time it argues, on page 12, that "the proposed rule does not apply to products like Anucort . . ." This selective, inconsistent application of authorities and principles is what has led to the complex legal arguments in this case.

Most significantly, however, whatever the Government's inconsistent positions as to the applicability of this Notice, the Notice clearly requires no bioequivalence data for any products (including suppositories) to support findings that they are "not new drugs." G & W agrees that this rule as applied in this Notice is also applicable to "products like Anucort."

2. G & W agrees with the Government that the *Hynson* case requires that there be adequate and well-controlled clinical studies establishing safety and effectiveness of Anucort to support general recognition of effectiveness among exports, and that *Generix* requires that these studies and the general recognition be applicable to the actual product involved and not just to its active ingredients, see brief, pp. 5-6. Both of these requirements are met in this case.

The affidavits submitted by G & W's experts rely on adequate and well-controlled clinical studies which in their opinions establish the safety and effectiveness of the Anucort product. The Government has not questioned that these studies are adequate and well controlled as required by *Hynson*. The uncontroverted expert affidavits further attest that the products on which these studies were conducted were such that, as a matter of fact, the studies establish the effectiveness of Anucort. *Generix* requires no more. Whether actual clinical studies showing bioequivalence are required for Anucort is at most a factual issue which must be determined at trial.

The government also argues that, as a matter of law, a showing of bioequivalence is always required before

clinical studies of another product may be relied upon to support "general recognition" of effectiveness among experts, citing 21 U.S.C. (Supp. IV) 355(j)(2)(A)(iv) (hereafter subparagraph A(iv)). This provision, which was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, sets the standards for FDA to apply in approving abbreviated new drug applications (ANDAs) for generic copies of drugs already approved by FDA. It does not apply to determinations of whether drugs are generally recognized as safe and effective, and there are significant legal and factual problems raised by an attempt arbitrarily to apply subparagraph A(iv) to this different statutory determination.[1]

An ANDA approval is based specifically on the safety and effectiveness of a designated, previously approved drug and there is thus good reason to ensure by a bioequivalence requirement that the specific data supporting that drug applies to generic copies of it. A general recognition determination under 21 U.S.C. 321(p), on the other hand, does not necessarily rely on data relating to one drug but may, as in the case of Anucort, may be based on clinical studies of a number of related drugs from which experts can fairly and responsibly conclude that the drug is generally recognized as safe and effective. Whether a showing of bioequivalence is necessary for a study of another product to be relevant to this determination of general recognition is a factual question, and there is no policy reason requiring such studies in all cases if in fact it is not scientifically necessary.

The enactment of subparagraph A(iv) did not, as the Government contends, answer the question which this Court left open in *Generix*, i.e., whether the FDA must

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[1] 21 U.S.C. 321(p) defining "new drug" was not amended in 1984 to incorporate any such bioequivalence study requirements into the determination of whether a product is "generally recognized" as safe and effective among experts.

make a factual showing that there is a reasonable possibility that a drug is not bioequivalent before the courts will impose a bioequivalence requirement in a determination of "new drug" status under 21 U.S.C. 321(p).

3a. The Government is also factually incorrect in its description of the provisions of subparagrph A(iv). Specifically, footnote 4 of the Government brief inaccurately states that there is only one exception, "not applicable here," to the requirement for bioavailability studies, i.e., the substitution of one active ingredient in a drug product containing more than one active ingredient. The exception in subparagraph A(iv) in fact applies whenever a petition is approved under 21 U.S.C. (Supp. IV) 355(j)(2)(C) (hereafter subparagraph C). Subparagraph C applies not only to petitions to substitute one active ingredient for another, but also to petitions to allow different routes of administration, dosage forms and strengths. In this case, the studies relied upon by G & W's experts in support of Anucort involve in some cases, different (but related) active ingredients, different (but related) dosage forms (creams, ointments, etc., rather than suppositories) and in some cases different (but related) dosage strengths, all of which could be covered by an approved petition under subparagraph C.

Thus, even if subparagraph A(iv) were to be applied to a determination of whether a product is a "new drug" the portion of it which would be applicable here is not the requirement of a bioequivalence study, but the exception for applications covered by an approved subparagraph C petition. The exception would only require information to show that the "active ingredients . . . are of the same pharmacological or therapeutic class as" the drug to which it is being compared, and that "it can be expected to have the same therapeutic effect" as the drug when administered to patients for the same conditions of use. This is precisely the kind of information which was provided by G & W's experts in their affidavits. Whether

this information on Anucort meets the statutory standard would of course be an issue of fact to be determined at trial.

3b. An additional reason why the bioequivalence requirement of subparagraph A(iv) does not properly apply here is that Anucort comes within a category of drugs for which FDA has by regulation waived the *in vivo* bioequivalence requirement.

The Government argues (brief, p.10) that FDA's regulation which waives bioavailability for topical drugs does not apply to a suppository like Anucort because it now (for this litigation) defines a topical drug as one which is applied directly to the site at which it is to have its effect. Based on this newly made up definition, they argue that a rectal suppository is not top[illegible] because it is not applied directly to the site of its external hemorrhoid indication. There are, however, mechanisms by which a rectal suppository can be directly applied to external hemorrhoids. It can be ~~effective, for~~ example, because the suppository melts, seeps down the anal canal, and spreads to cover the external sites. There is no evidence in the record which would dispute this conclusion. The Government quotes in footnote 8 of its brief from a comment made by FDA in the preamble of its 1988 Notice of Proposed Rulemaking rejecting this mechanism of application of suppositories to external sites as ineffective. However, this is merely a tentative position taken by FDA in an ongoing rulemaking proceeding. It confirms that there is a factual dispute about the effectiveness of this "seepage" mechanism, but it is not a reasonable basis for considering this factual issue to be resolved, as a matter of law, against G & W in this case.

Finally, the Government also argues that since it cannot waive the statutory requirement for bioequivalence in approving ANDAs for products which are admittedly "new drugs," that requirement must apply in determin-

ing whether a product is a "new drug". Whether or not this is an accurate reading of the statutory provision, it does not resolve the question of what type of showing must be made to establish bioequivalence. Indeed, despite this alleged inability to waive the requirement, FDA routinely waives any requirement for *in vivo* testing, accepting instead evidence as to formulation and compliance with good manufacturing practices. (See brief, fn. 6) No allegation has ever been made that Anucort fails to meet proper formulation or good manufacturing practice requirements. Moreover, any such question would again raise factual issues which would have to be resolved at trial.

CONCLUSION

This case involves significant questions as to the application of *Chevron* in cases in which the Government's litigating position is inconsistent with prior and subsequent agency actions, and presents important federal questions applicable to many existing products as to the data and information necessary to establish that a drug product is "generally recognized as safe and effective among experts." This petition for certiorari should therefore be granted.

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